Journal of Clinical Lipidology (2021) 000, 1–9

Journal of Clinical Lipidology

# Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience

**Rodrigo Alonso, MD, PhD*, Ovidio Muñiz-Grijalvo, MD, PhD, Jose Luis Díaz-Díaz, MD, PhD, Daniel Zambón, MD, PhD, Raimundo de Andrés, MD, PhD, Raquel Arroyo-Olivares, Francisco Fuentes-Jimenez, MD, PhD, Juan Sanchez Muñoz-Torrero, MD, PhD, Jose Cepeda, MD, PhD, Rocío Aguado, MD, PhD, Pilar Alvarez-Baños, MD, Marta Casañas, MD, Marta Dieguez, MD, María Dolores Mañas, MD, Patricia Rubio, MD. PhD, Rosa Argueso, MD, PhD, Francisco Arrieta, MD, PhD, Pablo Gonzalez-Bustos, MD, Leopoldo Perez-Isla, MD, PhD, Pedro Mata, MD, PhD**, on behalf of SAFEHEART investigators[1]**

*Fundación Hipercolesterolemia Familiar, General Alvarez de Castro 14, E 2800 Madrid, Spain; Center for Advanced Metabolic Medicine and Nutrition, Av. Las Condes 9460, of 501, Santiago, Chile; Internal Medicine Department, Hospital Virgen del Rocío, Sevilla, Spain; Internal Medicine Department, Hospital Abente y Lago, A Coruña, Spain; Lipid Unit, Hospital Clinic, Barcelona, Spain; Internal Medicine, Fundación Jiménez Díaz, Madrid, Spain; Lipid and Atherosclerosis Unit, CIBERObn, IMBIC, Hospital Universitario Reina Sofia, Córdoba, Spain; Internal Medicine Department, Hospital San Pedro de Alcántara, Cáceres, Spain; Internal Medicine Department, Hospital Comarcal Vega Baja, Orihuela, Spain; Department of Endocrinology, Hospital General de León, León, Spain; Department of Endocrinology, Hospital Universitario de Burgos, Burgos, Spain; Internal Medicine Department, Hospital San Pedro, Logroño, Spain; Department of Endocrinology, Hospital de Cabueñes, Gijón, Spain; Internal Medicine Department, Hospital Universitario, Ciudad Real, Spain; Internal Medicine Department, Hospital Jerez de la Frontera, Cadiz, Spain; Department of Endocrinology, Hospital Universitario Lucus Augusti, Lugo, Spain; Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain; Internal Medicine Department, Hospital Universitario Virgen de las Nieves, Granada, Spain; Department of Cardiology, Hospital Clínico San Carlos, IDISSC, Madrid, Spain*

Author's contributions: RA, OM, JLD, RAO, FFJ, LPI and PM, contributed to the concept and design of the work; acquisition, analysis, or interpretation of data.RA, OM, JLD, DZ, RAO, FFJ, JSMT, JC, RA, PAB, MC, MD, MDM, PR, RA, FA, PGB, LPI, PM drafted the article and revised critically. All authors approved this version, have participated sufficiently in the work and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest: RA received honorary fees for talks and advisory boards from Amgen, Sanofi, MSD, Tecnofarma, Abbott, Saval. OM received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen, and Sanofi. JLD received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen, and Sanofi. LP received honoraria for speaker or researcher activities from Merck Sharp and Dohme, AstraZeneca, Esteve, Amgen, and Sanofi. PM received honoraria for advisory boards and received research grants from Amgen and Sanofi.

Funding: This study was funded by the Fundación Hipercolesterolemia Familiar; grant G03/181 and FIS PI12/01289 of the Instituto de Salud Carlos III (ISCIII) and grant 08-2008 from the Centro Nacional de Investigación Cardiovascular (CNIC).

* Corresponding author at: Center for Advanced Metabolic Medicine and Nutrition, Av. Las Condes 9460, of 501, Santiago, Chile.

** Corresponding author.

E-mail addresses: ralonso@cammyn.cl (R. Alonso), pmata@colesterolfamiliar.org (P. Mata).

Submitted February 25, 2021. Accepted for publication April 26, 2021.

[1] For the SAFEHEART investigators (Complete list accessible at: https://www.colesterolfamiliar.org/en/safeheart-study/lipid-clinics-participating-in-the-study/).



https://doi.org/10.1016/j.jacl.2021.04.011

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

**Keywords**
familial hypercholesterolemia;
lipid-lowering treatment;
statins;
PCSK9 inhibitors;
LDL-C targets;
primary and secondary prevention

**Background:** PCSK9 inhibitors are a treatment option for patients with familial hypercholesterolemia not on low-density lipoprotein cholesterol goals despite the use of maximally tolerated high intensity-statins dose.

**Objective:** To evaluate the efficacy of alirocumab and evolocumab in LDL-C reduction and targets attainment in patients with heterozygous familial hypercholesterolemia in clinical practice setting.

**Methods:** SAFEHEART is an open, long-term prospective study of a cohort of subjects with molecular diagnosis of familial hypercholesterolemia. This study analyze subjects ≥ 20 years of age on stable lipid-lowering therapy, who received PCSK9 inhibitors during the period 2016 to January 2020.

**Results:** 433 patients (mean age 55 years, 53% male, 39% with cardiovascular disease) were included and followed-up for a median of 2.5 years (IQR 1.6–3.0). Median LDL-C level prior to PCSK9 inhibitors was 145 mg/dL (IQR 125–173). The addition of PCSK9 inhibitors (211 alirocumab, 222 evolocumab) reduced LDL-C by 58% (IQR 41–70) $p<0.001$, in men and women, achieving a median LDL-C level of 62 mg/dL (IQR 44–87) without differences between both PCSK9 inhibitors. Out of them 67% with and 80% without cardiovascular disease reached 2016 ESC/EAS LDL-C targets, and 46% very high risk and 50% high risk patients achieved 2019 ESC/EAS LDL-C goals. Independent predictor factors for attainment of 2019 ESC/EAS LDL-C goals were to be male, smoking and the use of statins with ezetimibe. Both inhibitors were well tolerated.

**Conclusions:** PCSK9 inhibitors on top of maximum lipid-lowering treatment significantly reduced LDL-C levels in patients with familial hypercholesterolemia and improved the achievement of LDL-C targets.



## Introduction

Familial hypercholesterolaemia (FH) is an autosomal co-dominant disorder clinically characterized by increased low-density lipoprotein (LDL)-cholesterol plasma levels, and the development of premature atherosclerotic cardiovascular disease (ASCVD). It is caused by loss-of-function variants in *LDLR* gene, and less frequently loss-of-function variants in *APOB* gene, and rarely gain-of function variants in *PCSK9* gene.[1,2]

According to 2016 European Guidelines for the management of dyslipidemias, FH patients are considered to be at high or very high cardiovascular risk and recommend an absolute LDL-C goal level of less than 100 mg/dL for patients without history of ASCVD and less than 70 mg/dL for those with history of ASCVD, or a reduction of at leats 50% from baseline LDL-C levels in both cases.[3] In the recent European Guidelines from 2019, FH patients with ASCVD or with another major risk factor are at very high risk and recommended targets are an LDL-C below 55 mg/dL and 50% reduction in LDL-C. Those patients in primary prevention without other risk factor are considered at high risk and LDL-C goals are a 50% reduction or more of LDL-C and an LDL-C below 70 mg/dL.[4]

Medical treatment of FH includes diet and lifestyle changes, and the use of high intensity statins, ezetimibe, and PSCK9 inhibitors (PCSK9i).[2,3] Patients with heterozygous FH often respond to these medications; however, most of them do not reach LDL-C goals and have a high residual risk of ASCVD. Data from different cross-sectional[5,6] and prospective observational[7,8] studies have shown that LDL-C goal attainment in heterozygous FH patients is below 20% despite the use of maximally tolerated high intensity-statins plus ezetimibe, regardless of whether patients are controlled in lipid clinics or in primary care. On the other hand, PCSK9i have been tested in FH patients in clinical trials under controlled circumstances showing a sustained 50% reduction in LDL-C levels and higher LDL-C goal achievement.[9,10]

Some international guidelines recommend the use of PCSK9i in patients with FH that have substantially higher LDL-C levels despite maximally tolerated statin with or without ezetimibe.[11] In real clinical practice, the use of PCSK9i is still low, partly explained by their cost and insurance coverage. In the current study, we aimed to investigate the use and efficacy of PCSK9i (Alirocumab and Evolocumab) as well as LDL-C goals achievement in clinical practice setting of FH patients registered and followed-up in the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) study.

## Patients and methods

### Patients

The SAFEHEART design and methodology have been previously described[11] Briefly, SAFEHEART is an open, multicenter, nationwide, long-term prospective study of a cohort of subjects with molecular diagnosis of FH.[12,13] The recruitment of families began in 2004 and the coordinating center of the study managed the follow-up of the patients. The patients are contacted on a yearly basis by using a standardized telephone survey to obtain relevant changes in life-style habits, adherence and tolerance to medication, and the presence of new cardiovascular events. Blood anal-

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

ysis during the follow-up are performed in local lipid units according local protocols and sent to the coordinating center. The definition of incidental ASCVD events have been previously reported.[14] A more detailed information about methods in SAFEHEART are available in Supplementary material. LDL-C goals were defined and analyzed according to the 2016 and 2019 European Dyslipidemia Guidelines.[3,4] Guidelines from 2016 were used to inform, educate, and train participating physicians in this cohort.

The choice of the particular PCSK9i and dosing regimen was at the discretion of the medical specialist. This study included all patients who were prescribed a PCSK9 monoclonal antibody (subcutaneous injection of alirocumab 75/150 mg every 2 or 4 weeks, or evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks) since its approval in Spain in 2016 until January 2020, and kept an stable dose of the inhibitors at least 3 months before the last analysis. Eligibility for PCSK9i was based according Spanish National Health System reimbursement regulations in FH patients when LDL-C levels are over 100 mg/dL with high intensity statin or maximal tolerated dose, or as monotherapy (or combined with Ezetimibe) in case of statin intolerance as defined and reported by their physician.[15] Moreover, in Spain medication is delivered by the hospital pharmacy every 3 months directly to the patient, ensuring access to it. Patients who participated in randomized clinical trials with PCSK9i before 2016 were not included in this analysis.

This study was approved by the local ethics committees, and all eligible subjects gave written informed consent.

## Variables

Demographic and clinical variables including age, classic cardiovascular risk factors (CVRF), physical examination and lipid-lowering therapy (LLT) were included. LDL-C was estimated by means of the Friedewald formula. The most recent lipid profile before the analysis was selected for this study. Lipoprotein (a) levels were measured once at inclusion in the study with a turbidimetric method (Quantia Lp(a) 7K00-01) in the centralized laboratory. Classification of LLT was defined as previously reported.[8] The genetic diagnosis and molecular classification of FH was performed as previously described[16] (Supplementary material). The SAFEHEART risk equation (SAF-RE) was estimated in each subject at initiation of PCSK9i and in the last control of follow-up.[14]

## Statistical analysis

Statistical analyses were carried out with the STATA program, version 12.0 (Stata Corporation, College Station, TX). Variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. A descriptive analysis was carried-out to report the number of cases and percentages for the qualitative variables, and the median and interquartile range (IQR) for the quantitative variables that did not follow a normal distribution. Comparisons of proportions between the qualitative variables were carried out using the Chi-square test and the binomial test to compare the proportion observed in each treatment group with the value of the total population. The median comparison for independent data was analyzed with the Mann–Whitney *U* test, and the median comparison of two dependent data was analyzed using the Wilcoxon signed-rank test. The association between PCSK9i treatment and LDL-C goal achievement as well as patient characteristics and CVRF (age, gender, body mass index (BMI), tobacco, hypertension, diabetes, LLT background, and LDL-C levels (categorized as $< 130$ mg/dL, 130 to 159 mg/dL and $> 160$ mg/dL) was first assessed by univariate logistic regression analysis. All significant variables were then included in a multivariable logistic regression analysis. A value of $p < 0.05$ was considered statistically significant.

## Results

Over the study period, a total of 443 patients $\geq 20$ years of age from 5033 subjects (3759 heterozygous FH and 1274 non-affected relatives) registered in the SAFEHEART initiated treatment with PCSK9i. Ten patients withdraw PCSK9i during the first 3 months due to their own decision (4 cases), physician decision due to low response (3 cases), side-effects (2 cases) and recent diagnosis of pancreatic cancer (1 case). For this analysis, 433 cases (211 with alirocumab and 222 with evolocumab) with a median follow-up of 2.5 years (IQR 1.6–3.0) were included. Characteristics of patients at initiation of PCSK9i and after the follow-up period are shown in Table 1. All cases have molecular diagnosis of FH and 51% carry variants in *LDLR* gene classified as null mutations. Median age at initiation of PCSK9i therapy was 55 years, 53% were male, and 39% had history of ASCVD. Most patients (93%) were receiving long-term maximal lipid-lowering therapy to reduce LDL-C levels over 50%, and 78% were with maximal combined therapy. Prior to starting PCSK9i, median LDL-C level was 145 mg/dL (IQR 125–173). There were no differences in cardiovascular risk factors and lipid levels according the PCSK9i prescribed at initiation of therapy (Supplementary Table 1). The estimated 5-year CV risk using the SAF-RE was 1.45% (IQR 0.73–4.50) prior to PCSK9i use and decreased to 0.57% (IQR 0.30–1.66) in the follow-up. Also, a significant 52% reduction in current smokers, 12% reduction in cases receiving maximal LLT and 22% in those with maximal combined therapy was observed in the follow-up.

Twenty-five patients received PCSK9i in monotherapy and 14 patients were also receiving ezetimibe because they had history of statin intolerance. Fifty-eight percent of patients treated with alirocumab received 75 mg every 2 weeks and 38% had 150 mg every 2 weeks. Few patients received alirocumab less frequently than recommended: 75 mg monthly ($n$=3) and 150 mg monthly ($n$=6). With respect to evolocumab, 90% of patients were treated with 140 mg every 2 weeks. Patients with history of ASCVD were more male

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

**Table 1** Characteristics of patients before receiving PCSK9i and in the follow-up in SAFEHEART.

| | Before | Follow-up | *P* |
|---|---|---|---|
| N | 433 | 433 | |
| Gender (male) | 228 (53) | 228 (53) | – |
| Age, years | 55 (47–64) | 56 (48–66) | <0.001 |
| BMI (kg/m$^2$) | 27 (25–30) | 27 (25–30) | 0.74 |
| ASCVD | 167 (39) | 176 (41) | 0.53 |
| Diabetes | 36 (8) | 47 (11) | 0.20 |
| Hypertension | 123 (28) | 137 (32) | 0.29 |
| Current smoker | 91 (21) | 44 (10) | <0.001 |
| Null allele variants | 222 (51) | 222 (51) | – |
| Maximal LLT | 402 (93) | 357 (82) | <0.001 |
| Maximal combined treatment | 337 (78) | 263 (61) | <0.001 |
| Years with statins | 18 (12–24) | 19 (14–25) | <0.001 |
| Years with ezetimibe | 9 (6–11) | 11 (7–12) | <0.001 |
| Total cholesterol | 219 (194–250) | 137 (113–165) | <0.001 |
| LDL-C | 145 (125–173) | 62 (44–87) | <0.001 |
| HDL-C | 49 (41–58) | 50 (43–59) | <0.001 |
| Triglycerides | 104 (77–139) | 95 (72–135) | 0.007 |
| Lp(a) | 34 (13–77) | NA | – |
| SAF-RE – 5 years | 1.45 (0.73–4.50) | 0.57 (0.30–1.66) | <0.001 |

BMI, Body mass index; ASCVD, atherosclerosis cardiovascular disease; LLT, Lipid-lowering treatment; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; Lp(a), Lipoprotein (a); SAF-RE, SAFEHEART risk equation. NA, not available; Continuous variables are expressed as median (IQR) and other variables are expressed as number (%). Lipid levels are in mg/dL.

**Table 2** Characteristics of patients prior to receive PCSK9i according the presence of cardiovascular disease.

| | ASCVD− (*n*=266) | ACVD+ (*n*=167) | *P* |
|---|---|---|---|
| Gender, male | 122 (46) | 106 (63) | <0,001 |
| Age, years | 53 (46–61) | 60 (53–67) | <0,001 |
| BMI, kg/m$^2$ | 27 (24–30) | 28 (26–31) | 0,002 |
| Diabetes | 12 (5) | 24 (14) | <0,001 |
| Hypertension | 52 (20) | 71 (43) | <0,001 |
| Current smoker | 64 (24) | 27 (16) | 0,052 |
| Null allele variants | 136 (60) | 86 (59) | 0,94 |
| Total cholesterol | 229 (202–258) | 206 (181–243) | <0,001 |
| LDL-C | 150 (132–180) | 134 (116–160) | <0,001 |
| HDL-C | 51 (44–60) | 45 (38–54) | <0,001 |
| Triglycerides | 102 (74–135) | 110 (83–141) | 0,097 |
| Lp(a) | 29 (12–68) | 48 (19–88) | <0.001 |

BMI, body mass index; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; Lp(a), Lipoprotein(a). Continuous variables are expressed as median (IQR) and other variables are expressed as number (%). Values of lipids levels are in mg/dL.

($p$<0.001), older ($p$<0.001), with hypertension ($p$<0.001) and type 2 DM ($p$<0.001) compared with those patients without ASCVD (Table 2).

The addition of PCSK9 inhibitors to background lipid-lowering therapy reduced LDL-C by 58% (IQR 41–70) $p$<0.001 in men and women with a median LDL-C level achieved of 62 mg/dL (IQR 44-87) without differences between both PCSK9 inhibitors. Of the total subjects, 67% with and 80% without cardiovascular disease reached an LDL-C target below 70 mg/dL and 100 mg/dL, respectively according to 2016 ESC/EAS guidelines. On the other hand, 125 patients (46%) considered as very high risk achieved an LDL-C goal < 55 mg/dL, and 81 patients (50%) considered as high risk achieved an LDL-C goal < 70 mg/dL according 2019 ESC/EAS guidelines.

A high inter-individual variability in the response to PCSK9i was observed (Figure 1). Thirty three patients (7.6%) had an LDL-C reduction below 15% and in 67 patients (15.5%) the response was below 30% (cut-off level considered as hypo-responders). These subjects were more female, youngers, with lower baseline LDL-C levels and treated less intensively (Supplementary Table 2). On the other hand, 106 patients (24.4%) had a reduction over 70%.

As alirocumab was used mainly in 2 different doses, a comparison between those patients treated with 75 mg or 150 mg every 2 weeks was performed. No differences were observed in gender, baseline Lp(a) levels, median achieved LDL-C levels, LDL-C goal attainment according presence or not of ASCVD, and percentage of hypo-responders among both doses (Supplementary Table 3). Only, the percent reduction in LDL-C was slightly higher with 150 mg scheme (63%; IQR 46–73 vs 57%; IQR 42–66, $P$=0.03).

A significant differential response was observed according to background LLT ($P$<0.005 between groups). The lower LDL-C achieved (55 mg/dL; IQR 39–75) and the higher percentage reduction (61%, IQR 49–73) were obtained when both PCSK9i were used on top of statin and ezetimibe. On the other hand, the median LDL-C achieved was higher (150 mg/dL, IQR 92–202), and the percentage reduction in LDL-C was lower (21%, IQR 8–38) when PCSK9i

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

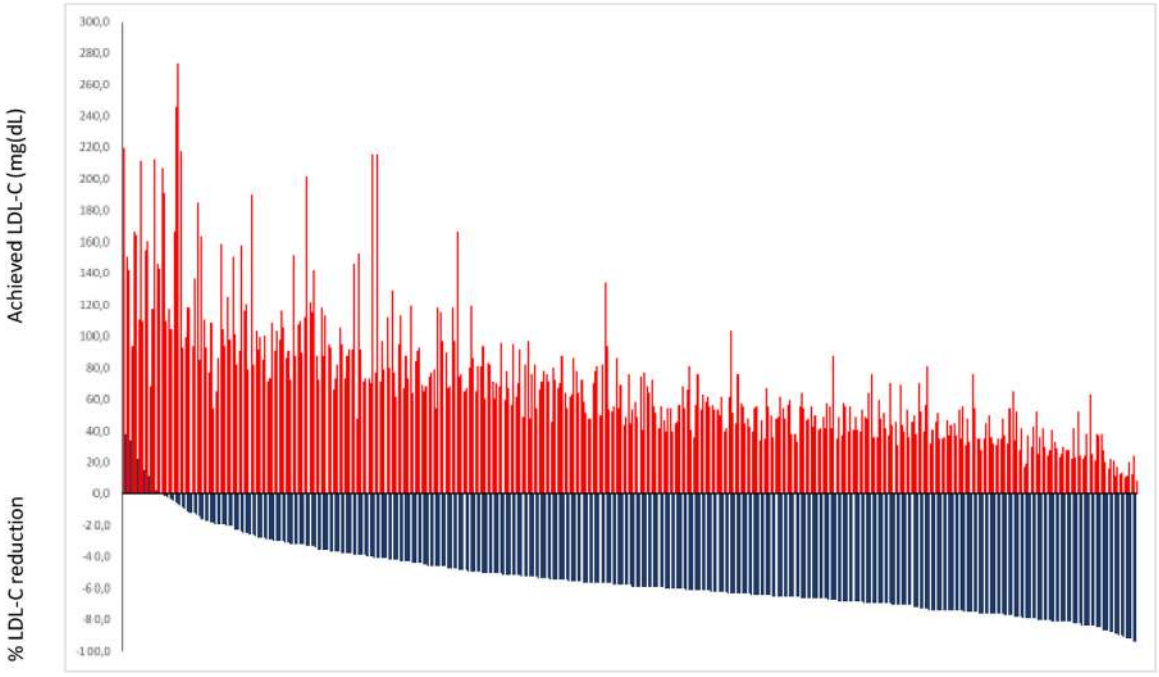


**Figure 1** Individual values of achieved LDL-C levels and percent reduction in LDL-C with PCSK9i.

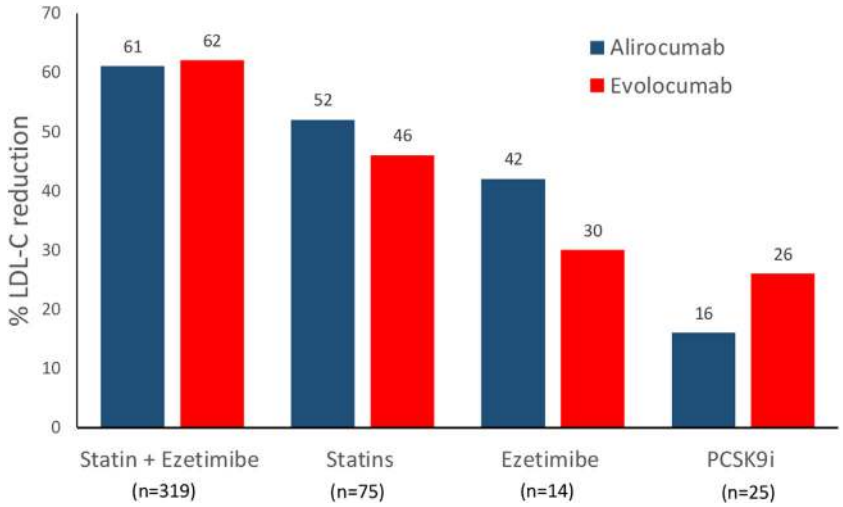


**Figure 2** LDL-C percent reduction according background Lipid-lowering therapy.

were used as monotherapy. Patients with statins or ezetimibe were between these 2 groups (Figure 2). There were no differences in the achieved LDL-C and percentage reduction in LDL-C according baseline LLT between alirocumab and evolocumab, and there were no differences in each treatment group according to the type of mutation.

In multivariate regression analysis, independent predictors for 2019 ESC/EAS LDL-C goals attainment were to be male ($P$=0.023), smoker ($P$=0.041), and the use of statins with ezetimibe ($P$=0.008). On the other hand, higher LDL-C levels prior to initiation of PCSK9i showed a significant inverse relationship with goals attainment (Table 3). Predictors for 2016 ESC/EAS goal attainment are shown in Supplementary Table 4.

In the follow-up period after initiation of PCSK9i, nine patients had a cardiovascular event with an estimated incidence rate of 1.39 events/100 patients-year. Prior to initiation of PCSK9i, these patients were older (64 years, IQR 62–70), smokers (33%), had more hypertension (44%), and higher LDL-C levels (171 mg/dL; IQR 138–191) compared with those patients that did not suffered any cardiovascular event in the follow-up. None of the patients had history of clinical ASCVD and none reached 2 years of treatment with PCSK9i (range 2 months to 1.5 years).

With the exception of 10 patients that discontinued PCSK9i during the first 3 months, no other patient discontinued treatment by safety issues in the median 2.5 years of follow-up. Both alirocumab and evolocumab were

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

**Table 3** Logistic regression analysis. Combined LDL-C goal achievement, LDL-C < 55 mg/dL in very high risk, and < 70 mg/dL in high risk patients according 2019 ESC/EAS guidelines.

| | Univariate regression analysis | | | Multivariate regression | |
|---|---|---|---|---|---|
| Variable | OR (95% CI) | *Z* | *P* | OR (95% CI) | *P* |
| Age | 1.00 (0.98–1.02) | 0.45 | 0.656 | | |
| Gender (male) | 1.78 (1.22–2.62) | 2.98 | 0.003 | 1.60 (1.06–2.40) | 0.023 |
| BMI | 0.97 (0.93–1.01) | −1.09 | 0.276 | | |
| Hypertension | 1.03 (0.69–1.55) | 0.17 | 0.865 | | |
| ASCVD | 1.14 (0.77–1.69) | 0.70 | 0.483 | | |
| Current smoker | 0.42 (0.21–0.83) | −2.47 | 0.014 | 0.47 (0.22–0.97) | 0.041 |
| *Background LLT* | 21.64 (2.88–162.5) | 2.99 | 0.003 | 15.40 (2.01–117.85) | 0.008 |
| Statins + Ezetimibe Statins only | 8.39 (0.82–85.22) | 1.80 | 0.072 | 6.51 (0.62–68.10) | 0.117 |
| Ezetimibe Statins (all)* | 10.49 (0.45–239.78) | 1.47 | 0.141 | 7.31 (0.30–177.56) | 0.221 |
| | 6.35 (2.42–16.68) | 3.76 | <0.0001 | | |
| LDL-C (1 mg/dL increase) | 0.99 (0.98–0.99) | −3.55 | <0.0001 | | |
| LDL-C 130–159 mg/dL LDL-C > | 0.74 (0.46–1.19) | −1.23– | 0.218 | 0.76 (0.46–1.23) 0.37 | 0.272 |
| 160 mg/dL | 0.32 (0.19–0.52) | 4.59 | <0.0001 | (0.22–0.61) | <0.0001 |
| Lp(a) | 1.00 (0.99–1.00) | 0.57 | 0.570 | | |
| Lp(a)>50 mg/dL | 1.12 (0.76–1.65) | 0.60 | 0.549 | | |

BMI, body mass index; ASCVD, atherosclerosis cardiovascular disease; LLT, lipid lowering therapy; (*) statin treatment was considered with and without ezetimibe.

well tolerated and doses were not modified in any patient. A small number of patients reported mild injection site reaction.

## Discussion

This study, the largest reported to the best of our knowledge in routine clinical practice of patients with heterozygous FH with two monoclonal antibodies to PCSK9, shows that the addition of alirocumab or evolocumab to FH patients on maximal LLT over a median of 2,5 years, effectively reduced LDL-C levels of roughly 60% both in men and women, similar to the reduction observed in randomized clinical trials (RCT). Additionally, a higher percentage of patients with ASCVD and without ASCVD achieved LDL-C goals, 66% and 80% respectively, without differences among patients receiving alirocumab or evolocumab. Independent predictor factors for attainment of LDL-C goals were to be male and the use of high intensity statins with ezetimibe (ESC/EAS 2019 guidelines) or with and without ezetimibe (ESC/EAS 2016 guidelines). Interestingly, different LDL-C reduction according to background lipid lowering treatment was observed with both PCSK9i.

Previous report of the SAFEHEART study showed a modest improvement in LDL-C goal achievement in FH patients with ASCVD up to 5% and up to 22% in those patients without ASCVD after 5 years of follow-up due to an improvement in conventional LLT, without inclusion of PCSK9i at that moment.[8] This is in line with other study in molecularly defined FH population in Norway.[17] These findings show the difficulty in reducing LDL-C in patients with FH as they usually have higher baseline LDL-C levels, and that the addition of PCSK9i to background maximal LLT could be the best option in this population.

Median LDL-C reduction of 58% with PCSK9i in this cohort was comparable with those observed in RCT with evolocumab and alirocumab in FH patients, in long-term open label studies, and in some short-term experience in clinical setting.[18–26] In the RUTHEFORD II trial with evolocumab,[18] and in the Odissey FH I and FH II trial with alirocumab,[19] mean LDL-C reduction was 58% to 61% in FH patients with stable high intensity statin and ezetimibe. In the recent publication of the Taussig trial, severe FH patients with mean LDL-C level of 193 mg/dL on stable LLT had 47% LDL-C reduction with evolocumab after a median of 4,1 years of follow-up, with a high inter-individual variation in the response.[22] In the open-label extension study with alirocumab (Odissey OLE), FH patients on maximally tolerated statin dose (58% with ezetimibe) and mean LDL-C level of 124 mg/dL, had a 48% reduction in LDL-C after a median of 2.5 years.[10] In these studies, the effect of background LLT or the effect of the type of mutation on PCSK9i response in heterozygous FH were not analyzed. On the other hand, there are few studies including FH patients in a clinical practice environment assessing the efficacy of PCSK9i. Some of them were performed in a single center,[23,24] with retrospective analysis,[25] most cases diagnosed as FH trough clinical criteria,[24,26] including only one PCSK9i,[25,26] and with short period of follow-up (up to 12 weeks).[24–26] Stoekenbroek et al. reported efficacy and safety of PCSK9i in 160 heterozygous FH patients unable to achieve lipid goals with maximally tolerated statin therapy.[23] Mean LDL-C reduction was 54.6% without differences between both PCSK9i. In the

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

Japanese experience, Yokoto et al. reported 54% reduction in LDL-C after 12 weeks of treatment with evolocumab in a cohort of 320 FH patients with clinical diagnosis.[26] Barrios et al, retrospectively analyzed 186 patients (66 with molecularly defined FH) treated with evolocumab during 12 weeks. Mean LDL-C reduction was 57.5%, however no specific data for the FH group is reported.[25]

Our study has some differences with the results commented above. In the SAFEHEART all patients have molecular confirmation of the disorder permitting to make a better comparison in the response according to the genotype. We found no differences in the response independently of the type of mutation, confirming that PCSK9i long-term effect in heterozygous FH is similar to non-FH populations unlike the observed in homozygous FH patients with both affected alleles.[27,28] On the other hand, most patients in our study were on maximal LLT using high intensity statin and ezetimibe, and few cases were only with ezetimibe or with PCSK9i in monotherapy. We found a significant differential response in LDL-C reduction according background LLT, being higher in those patients with statin and ezetimibe and lower in those intolerant statin patients with PCSK9i and ezetimibe and PCSK9i in monotherapy. Although the number in the latter group is small, the observed 21% reduction in LDL-C is smaller than the reduction in non FH statin intolerant patients.[29,30] Considering that patients at SAFEHEART are followed-up frequently and adherence to PCSK9i treatment is optimal according to the follow-up survey and the requirements for the prescription at hospital level, these results highlight the importance of adding other non-statin therapy like ezetimibe in patients with contraindication or who are intolerant to statins.

Although most patients respond to PCSK9i with marked reduction in LDL-C levels, we didn't find differences between males and females, as it has been shown in an analysis of the Fourier trial with a greater reduction in men.[31] However, a high inter-individual response to PCSK9i was observed as it has been shown for statins in non-FH populations[32] and PCSK9i. In our study, 8% to 15% of our patients can be considered hyporesponders to PCSK9i if a reduction in LDL-C below 15% or 30% is used as a criterion. These patients were more females, slightly youngers and most of them were not on maximal combined LLT . In RCT, the frequency of hyporesponders (< 15% LDL-C reduction) is between 1% and 5%.[20,33] Recently, Warden et al. showed that 10% of FH patients have an unusual response to PCSK9i, defined as a response below 30%.[34] Explanations for this poor response are not fully understood.[31–33] It may be related to baseline the type of *LDLR* mutation; however, we did not find any relationship in the response to PCSK9i with the genotype. Another possible explanation may be related to the presence of anti-drugs antibodies; however, this is an event that occurs in few patients in long-term trials with both PCSK9i, without evidence of neutralizing antibodies.[10,22,35]

A significant and impressive improvement in LDL-C goal achievement was observed in this population. According 2016 European guidelines,[3] patients in primary prevention reaching an LDL-C below 100 mg/dl increased from 3% to 80% and those in secondary prevention reaching an LDL-C below 70 mg/dL increased from 0.6% to 67%, being the gender and background LLT with statins (with or without ezetimibe) the most important predictors. Moreover, according recent guidelines,[4] 46% of patients classified as very high risk and 50% of high risk achieved an LDL-C below 55 mg/dL and 70 mg/dL, respectively. Our study supports that PSCK9i satisfy the unmet need for additional LDL-C reduction in FH patients. Long-term cardiovascular outcomes trials have shown their benefit and safety in high risk patients.[36,37] Predicting which patients with FH are likely to benefit from PCSK9 inhibitors might be possible by applying suitable risk-prediction models like the SAFEHEART risk equation[14,38] making the use of these drugs in FH potentially cost-effective in both primary and secondary ASCVD prevention.

## Study limitations

This is a multicenter nation-wide study analyzing a well-defined FH cohort followed-up prospectively in lipid clinics. The prescription of both PCSK9i was at the discretion of the physician, and they were distributed in the same number and characteristics.

The limitations of this study include the lack of blinding randomization, follow-up analysis are not centralized and Lp(a) measurement in the follow-up is not available. Therefore, the prospective impact of PCSK9i reduction therapy use in participants with elevated Lp(a) level was not evaluated in this study.

## Conclusions

PCSK9i on top of maximum lipid-lowering treatment significantly reduced LDL-C levels by 58% and improves the achievement of LDL-C targets without differences among alirocumab or evolocumab in FH patients in clinical practice. Independent predictor factors for attainment of LDL-C goals were to be male, smoking and the use of statins with ezetimibe. These results support and expand upon those reported previously in smaller studies with PCSK9i in heterozygous FH, although the clinical value and cost effectiveness of this new treatment have yet to be fully demonstrated**.**

## Acknowledgments

The authors thank Ms Teresa Pariente for her hard work managing the familial cascade screening from the beginning of the SAFEHEART registry and all the Spanish Familial Hypercholesterolemia Foundation for assistance in the recruitment and follow-up of participants and to the FH fami-

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

lies for their valuable contribution and willingness to participate.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2021.04.011.

## References

1. Watts G, Gidding S, Mata P, et al. Familial hypercholesterolemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol*. 2020;17:360–377.
2. Nordestgaard BG, Chapman MJ, Humphries SE, et al. for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J*. 2013;34:3478–3490.
3. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
5. Pijlman AH, Huijgen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with Familial hypercholesterolemia: a large cross sectional study in the Netherlands. *Atherosclerosis*. 2010;209:189–194.
6. Béliard S, Carreau V, Carrié A, et al. Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: can we do better? Analysis of results obtained during the past two decades in 1669 French subjects. *Atherosclerosis*. 2014;234:136–141.
7. Pérez de Isla L, Arroyo-Olivares R, Muñiz-Grijalvo O, et al. Long-term effect of 2 intensive statin regimes on treatment and incidence of cardiovascular events in familiar hypercholesterolemia: the SAFEHEART study. *J Clin Lipidol*. 2019;13:989–996.
8. Perez de Isla L, Alonso R, Watts G, et al. Attainment of LDL–cholesterol treatment goals in patients with familial Hypercholesterolemia. 5 years SAFEHEART registry follow-up. *J Am Coll Cardiol*. 2016;67:1278–1285.
9. Hovingh K, Raal F, Dent R, et al. Long-term safety, tolerability, and efficacy of Evolocumab in patients with heterozygous familial hypercholesterolemia. *J Clin Lipidol*. 2017;11:1448–1457.
10. Farnier M, Hovingh K, Langslet G, et al. Long- term safety and efficacy of alirocumab in patients with heterozygous familial hypercholesterolemia: an open-label extension of the ODYSSEY program. *Atherosclerosis*. 2018;278:307–314.
11. Landmesser U, Chapman MJ, Stock JK, et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J*. 2018;39:1131–1143.
12. Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis*. 2011;10:94.
13. Pérez de Isla L, Alonso R, Mata N, et al. Coronary heart Disease, Peripheral arterial disease, and stroke in familial hypercholesterolemia. Insights from the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Arterioscler Thromb Vasc Biol*. 2016;36:2006–2010.
14. Pérez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation*. 2017;135(22):2133–2144.
15. Stroes ES, Thompson PD, Corsini A, et al. European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Etiology and Management. *Eur Heart J*. 2015;36:1012–1022.
16. Bourbon M, Alves AC, Alonso R, et al. Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: the SAFEHEART registry. *Atherosclerosis*. 2017;262:8–13.
17. Bogsrud MP, Græsdal A, Johansen D, et al. LDL-cholesterol goal achievement, cardiovascular disease, and attributed risk of Lp(a) in a large cohort of predominantly genetically verified familial hypercholesterolemia. *J Clin Lipidol*. 2019;13:279–286.
18. Raal F, Stein E, Dufour R. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385:331–340.
19. Kastelein JJP, Ginsberg H, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36:2996–3003.
20. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol–lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia. The reduction of LDL-C with PCSK9 inhibition in heterozygous. Familial hypercholesterolemia disorder (RUTHERFORD) RANDOMIZED TRIal. *Circulation*. 2012;126:2408–2417.
21. Ginsberg H, Rader D, Raal F, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016;30:473–483.
22. Santos R, Stein E, Hovingh K, et al. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol*. 2020;75:565–574.
23. Stoekenbroek R, Hartgers M, Rutte R, de Wijer D, Stroes E, Hovingh K. PCSK9 inhibitors in clinical practice: delivering on the promise? *Atherosclerosis*. 2018;270:205–210.
24. Ceballos-Macias JJ, Lara-Sanchez C, Flores-Real J, et al. PCSK-9 inhibitors in a real-world setting and a comparison between alirocumab and evolocumab in heterozygous FH patients. *J Endocrin Soc*. 2020;5(1) Nov 18bvaa180. Doi:10.1210/jendso/bvaa180.
25. Barrios V, Escobar C, Arrate V, et al. First National registry on the effectiveness and safety of evolocumab in clinical practice in patients attended in Cardiology in Spain. The RETOSS-CARDIO study. *Cin Invest Arterioscler*. 2020;32:231–241.
26. Yokote K, Ako J, Kitagawa K, et al. 12-weeks effectiveness and safety of Low-density lipoprotein cholesterol-lowerig therapy by Pproprotein Convertase Subtilisin/Kexin type 9 inhibition in patients with familial hypercholesterolemia and hypercholesterolemia. Data from a real-world observational study of Evolocumab in Japan. *Circ Rep*. 2019;1:219–227.
27. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–350.
28. Bloom D, Harada-Shiba M, Rubba P, et al. Efficacy and safety of Alirocumab in adults with Homozygous Familial Hypercholesterolemia. The ODYSSEY HoFH Trial. *J Am Coll Cardiol*. 2020;76:131–142.
29. Moriarty P, Thompson P, Cannon C, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–779.
30. Cho L, Dent R, Stroes E, et al. Persistent safety and efficacy of evolocumab in patients with statin intolerance: a subset analysis of the OSLER open-label extension studies. *Cardiovasc Drugs Ther*. 2018;32:365–372.

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011

31. Sever P, Gouni-Berthold I, Keech A, et al. LDL-Cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the Fourier trial. *Eur J Prev Cardiol*. 2020 Feb 4:2047487320902750. doi:10.1177/2047487320902750.
32. De Bacquer D, De Smedt D, Reiner Z, et al. Percentage low-density lipoprotein-cholesterol response to a given statin dose is not fixed across the pre-treatment range: real world evidence from clinical practice: data from the ESC-EORP EUROASPIRE V study. *Eur J Prev Cardiol*. 2020;27:1630–1636.
33. Bays H, Rosenson R, Baccara-Dinet MT, Louie M, Thompson D, Hovingh GK. Assessment of the 1% of patients with consistent < 15% reduction in low-density lipoprotein cholesterol: pooled analysis of 10 phase 3 ODYSSEY alirocumab trials. *Cardiovasc Drugs Ther*. 2018;32:175–180.
34. Warden B, Miles J, Oleaga C, et al. Unusual responses to PCSK9 inhibitors in a clinical cohort utilizing a structured follow-up protocol. *Am J Prev Cardiol*. 2020. doi:10.1016/j.ajpc.2020.100012.
35. Shapiro M, Miles J, Tavori H, Fazio S. Diagnosing resistance to a proprotein convertase subtilisin/kexin type 9 inhibitor. *Ann Intern Med*. 2018;168:376–379.
36. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
37. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.
38. Perez de Isla L, Ray K, Watts G, et al. Potential utility of the SAFE-HEART risk equation for rationalising the use of PCSK9 monoclonal antibodies in adults with heterozygous familial hypercholesterolemia. *Atherosclerosis*. 2019;286:40–45.

Please cite this article as: Alonso et al, Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: A clinical practice experience, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2021.04.011